Supplementary Materials

Electrostatic Free Energies and its Salt Sensitivities for a Set of 55 Proteins Based on the Linear and Nonlinear ACG-PB Solution

Electrostatic calculations for a series of 55 small to medium-sized proteins (ranging from 145 to 3564 atoms), with net charges varying from -25e to 11e, were carried out using the linear and nonlinear versions of the ACG-based PBE solver. The objective of these calculations is to: (i) compare the ACG-based PB predictions of the electrostatic solvation free energy against similar PB results obtained with the popular APBS-PB code for the same set of proteins; (ii) compare the computation times required to solve the linear and nonlinear PBE; (iii) confirm that relation (23) in the main text holds in its numerical implementation for realistic biomolecular geometries; (iv) contrast the electrostatic energy salt sensitivities, $dG^{el}/d\kappa$, obtained with the linear and nonlinear forms of the PBE; (v) examine nonlinear effects for proteins of varying charge distributions and shapes and; (vi) make available a collection of protein structures along with atomic radii and charges, and attendant results as a resource for future algorithmic development and benchmarking purposes.

A van der Waals surface description is adopted for the dielectric interface separating the solute and solvent regions. The Protein Data Bank (PDB) identification numbers (ids) of all 55 proteins are given in Table 1 along with their net charges. The protein atomic coordinates, radii and charges were the same as those used in the PB study of Tjong and Zhou[1] and associated input files are available at http://gbr6.sourceforge.net/. The physical environment was characterized by T=298K and dielectric constants, ε_1=1 and ε_2=80. The salt concentration ranges from 0.1 M to 0.5 M NaCl. No ion exclusion region was modeled in these PB calculations. The surface mesh spacing resolution was set to 0.3Å and the outer boundary set to approximately three times the largest molecular dimension.

Figure 1 compares the electrostatic solvation free energies of all 55 proteins at 0.5 M NaCl obtained on the basis of the linear PBE using the ACG-solver and the popular APBS solver with a 225^3 grid with a spacing of ~0.3 Å. Identical dielectric constants, molecular surface definition, atomic charges and radii were employed in both PB solvers. The excellent agreement between the ACG- and APBS-based electrostatic solvation free energies (note that the slope of the line obtained by a linear least square fit is 1.0 and R^2=0.9999) confirms that the ACG-PB solver accurately reproduces the electrostatic solvation energy predictions of very well established PBE solvers.

Next CPU costs incurred in solving the linear and nonlinear PBE are compared by computing the electrostatic solvation free energies at 0.1 NaCl. Figure 2 reports the CPU cost on a per atom basis which is seen to fluctuate around 0.15s for all proteins. Figure 3 compares the CPU times obtained with the linear and nonlinear PBE; solving the nonlinear PBE incurs, on average, a 6% increase in computation time over solving the linear PBE.

In order to extract the salt derivative of the electrostatic free energy using finite-differencing techniques, the biomolecules were analyzed with the ACG-PBE code at ionic strengths of $\{I_1,I_2,I_3\}=\{0.2M, 0.25M, 0.30557M\}$. These values produce equally spaced values of κ so that the finite difference approximation of the salt sensitivities of G^{el}:

$$\left(\frac{dG^{el}}{d\kappa}\right)^{FD}_{I=I_2} \cong \frac{G^{el}_3 - G^{el}_1}{\kappa_3 - \kappa_1} \tag{1}$$

is second order accurate. Here the subscripts refer to the given salt conditions. These estimates of the electrostatic energy salt sensitivities are depicted in Figure 4 and listed in Table 1 under the heading "FD of G^{el}". The salt sensitivities of G^{el} calculated directly using (23) from the main text are listed under the heading "ACG" and are seen to be in close agreement with the FD estimates indicating that the ACG-PBE enforces this internal consistency check reasonably well. The corresponding electrostatic free energy salt sensitivities obtained using the linear PBE (note that for the linear case the salt sensitivity of G^{el} can be evaluated using only the reaction field energy contribution) are listed under the heading "Linear" and are seen to differ significantly (60%-80% in some cases) from the nonlinear PBE results in several cases. These differences are typically most pronounced for proteins with high net charge, but also occur (less frequently) for systems with smaller net charge. For example, the difference between the linear and nonlinear results for tetrameric lectin (PDB code: 2chh, net charge: -3e), is much more pronounced than that for the B type DNA polymerase from *Archea Thermococcus Grogonarius* (PDB id: 1tg0), which has a larger net charge of -12e. This is expected for general systems since proximity of a charge to the surface as well as its charge value are what affect the magnitude of the potential at the surface and hence the significance of nonlinear terms. Generally, the linear PBE can either under- or over-predict the values of the derivative of G^{el} obtained using the nonlinear PBE. Thus, one should not gauge the importance of the nonlinearity simply on the basis of net charge.

References

1. Tjong, H., and Zhou, H.-X. (2006) The dependence of electrostatic solvation energy on dielectric constants in Poisson-Boltzmann calculations, *J. Chem. Phys. 125*, 206101-1- 206101-2

Table 1. Electrostatic energies and their salt sensitivities, with respect to the Debye-Hückel parameter, κ, computed for a collection of proteins (identifying by their PDB ids) with varying net charges and shapes using the ACG-PBE at I=0.25M. All electrostatic energies are in units of kcal/mol.

PDB id	Net Charge	G^{el}	G_{coul}	G_{rf}	G_m	$\Delta\Pi$	$dG^{el}/d\kappa$			Diff.
							ACG	FD of G^{el}	Linear	
1a6m	2	-44889.4	-42175.5	-2715.86	5.70204	-3.76799	-46.2825	-49.4488	-42.0522	-9%
1aho	-2	-20672.6	-19375.9	-1297.76	3.10223	-2.04385	-25.1048	-26.1788	-25.1134	0%
1byi	-4	-66875	-63298.4	-3579.64	8.63093	-5.54134	-68.0647	-72.7188	-67.3511	-1%
1c75	-4	-20131.3	-18731.1	-1400.74	2.18998	-1.59219	-19.557	-20.3613	-19.5505	0%
1c7k	-5	-44831.1	-42389.8	-2443.94	6.54143	-3.97359	-48.8078	-52.3575	-58.7565	**20%**
1cex	1	-64484.1	-61620.4	-2865.13	5.04762	-3.63128	-44.6033	-46.54	-42.849	-4%
1eb6	-15	-56127	-50999.2	-5131.75	10.4893	-6.53321	-80.248	-84.3538	-114.004	**42%**
1ejg	0	-12356.3	-11781.2	-575.739	1.50524	-0.91016	-11.1796	-11.635	-9.3658	-16%
1etl	0	-2871.67	-2581.4	-290.825	1.19243	-0.63287	-7.77363	-7.85363	-8.05969	4%
1exr	-25	-50136.9	-40771.2	-9374.27	19.1434	-10.5468	-129.547	-133.803	-237.743	**84%**
1f94	1	-20822.6	-19615.2	-1208.38	2.62626	-1.71419	-21.0556	-23.27	-19.1845	-9%
1f9y	-5	-52092.1	-49181.9	-2912.36	6.32156	-4.11673	-50.566	-55.2663	-47.6016	-6%
1g4i	-1	-39470.4	-37071.1	-2401.94	6.95686	-4.39583	-53.9943	-58.175	-55.6867	3%
1g66	-2	-58659.5	-55686.5	-2977.38	9.59416	-5.23838	-64.3435	-69.8101	-101.438	**58%**
1gqv	7	-49301.6	-46744.1	-2559.41	5.50604	-3.62651	-44.5447	-46.54	-46.0614	3%
1hje	1	-3190.26	-2913.13	-277.273	0.484203	-0.33798	-4.15147	-4.654	-3.72587	-10%
1iqz	-17	-23801.6	-19170.4	-4633.55	7.58045	-5.26524	-64.6734	-66.9013	-78.3953	21%
1iua	-1	-24848.8	-23561.8	-1287.75	2.56655	-1.79996	-22.109	-23.27	-21.8318	-1%
1j0p	8	-29872.4	-27058.9	-2815.05	5.39899	-3.85542	-47.3565	-49.4488	-46.6981	-1%
1k4i	-6	-69456.5	-65568.7	-3891.24	9.38668	-5.94128	-72.9772	-78.5363	-84.6179	16%
1kth	0	-18148.6	-16694.1	-1454.49	2.43364	-2.43364	-29.8926	-29.0875	-29.8926	0%
1l9l	11	-31527.7	-28432.3	-3097.17	5.922	-4.16746	-51.1892	-52.3575	-59.3602	16%
1m1q	-7	-26806.3	-24428.7	-2378.78	4.27567	-3.14036	-38.5732	-40.7225	-38.842	1%
1nls	-7	-71477.5	-66751.3	-4732.06	13.6295	-7.71786	-94.7991	-101.806	-169.212	**78%**
1nwz	-6	-38187.3	-35458.5	-2730.88	6.10417	-4.04759	-49.7168	-52.3575	-50.2902	1%
1od3	-3	-39304	-37273.1	-2032.73	4.7714	-2.95276	-36.269	-37.8138	-40.8299	13%
1ok0	-5	-22828.6	-21283	-1546.77	3.30567	-2.19137	-26.9168	-29.0875	-31.6749	18%
1p9g	4	-12654.2	-11908	-746.908	1.74507	-1.10964	-13.6298	-14.5438	-14.2405	4%
1pq7	4	-66929.7	-64364	-2567.45	5.25379	-3.5224	-43.2659	-46.54	-41.2281	-5%
1r6j	0	-24145.4	-22811.7	-1334.41	2.23408	-1.60236	-19.6819	-20.3613	-17.544	-11%
1ssx	8	-62837.6	-60219	-2619.77	4.13834	-3.0028	-36.8836	-40.7225	-36.5092	-1%
1tg0	-12	-20939.5	-17730.5	-3210.94	5.98293	-4.01032	-49.259	-49.4488	-63.0096	**28%**
1tqg	-7	-34743.8	-31830.2	-2915.57	6.32518	-4.32388	-53.1105	-55.2663	-59.4057	12%
1tt8	1	-57635.8	-55035.6	-2601.91	5.46842	-3.74604	-46.0128	-49.4488	-42.7438	-7%

1u2h	4	-35207	-33174.9	-2033.05	3.62067	-2.67859	-32.9013	-34.905	-32.3584	-2%
1ucs	0	-19003.4	-17982.6	-1021.49	2.16368	-1.52123	-18.6853	-20.3613	-17.6875	-5%
1ufy	-3	-41849.5	-39563	-2288.15	5.12747	-3.51995	-43.2358	-46.54	-43.0772	0%
1unq	-3	-43077.6	-39658.3	-3422.51	8.93632	-5.71496	-70.1972	-72.7188	-84.2531	**20%**
1vb0	3	-20794.3	-19694.7	-1100.04	1.56331	-1.13205	-13.9051	-14.5438	-12.6721	-9%
1vbw	8	-23127.9	-21318	-1810.94	3.46332	-2.45876	-30.2011	-31.9963	-31.8467	5%
1w0n	-5	-35030.5	-32601.3	-2432.08	6.81829	-3.89814	-47.8812	-49.4488	-59.8349	**25%**
1wy3	1	-5473.47	-5167.39	-306.365	1.15385	-0.87548	-10.7536	-10.4715	-10.5799	-2%
1x6z	0	-36999.8	-34842.4	-2158.87	4.42277	-2.96643	-36.4369	-37.8138	-35.7604	-2%
1x8q	-1	-56831.1	-53271.1	-3564	9.58528	-5.67773	-69.74	-75.6276	-84.9734	**22%**
1xmk	1	-26664.6	-25075.2	-1590.36	3.23532	-2.21238	-27.1749	-29.0875	-26.0977	-4%
1yk4	-8	-16054.5	-14173.4	-1882.01	3.23381	-2.31586	-28.4459	-29.0875	-29.5543	4%
1zzk	1	-25899.1	-24311.1	-1589.11	3.68428	-2.55727	-31.4111	-31.9963	-31.3099	0%
2a6z	-3	-75189.8	-71566.4	-3625.88	7.56598	-5.10669	-62.7259	-66.9013	-61.9247	-1%
2bf9	-2	-13638.9	-12730	-909.265	1.61304	-1.23486	-15.1679	-14.5438	-15.1038	0%
2chh	-3	-34133.3	-31994.9	-2140.91	5.42915	-2.95923	-36.3484	-40.7225	-59.8415	**65%**
2cws	-3	-69503.5	-66310.6	-3195.57	7.62143	-5.01273	-61.5718	-63.9926	-57.8821	-6%
2erl	-6	-12997.2	-11825.9	-1171.77	1.90569	-1.44408	-17.7378	-17.4525	-18.5809	5%
2fdn	-8	-15447.1	-13736.8	-1711.37	3.82283	-2.76263	-33.9335	-34.905	-36.8414	9%
2fwh	-6	-37562.1	-35312.7	-2250.66	3.95087	-2.75988	-33.8999	-37.8138	-33.6093	-1%
3lzt	8	-44439.7	-41850.8	-2590.81	5.79075	-3.84697	-47.2526	-52.3575	-46.577	-1%

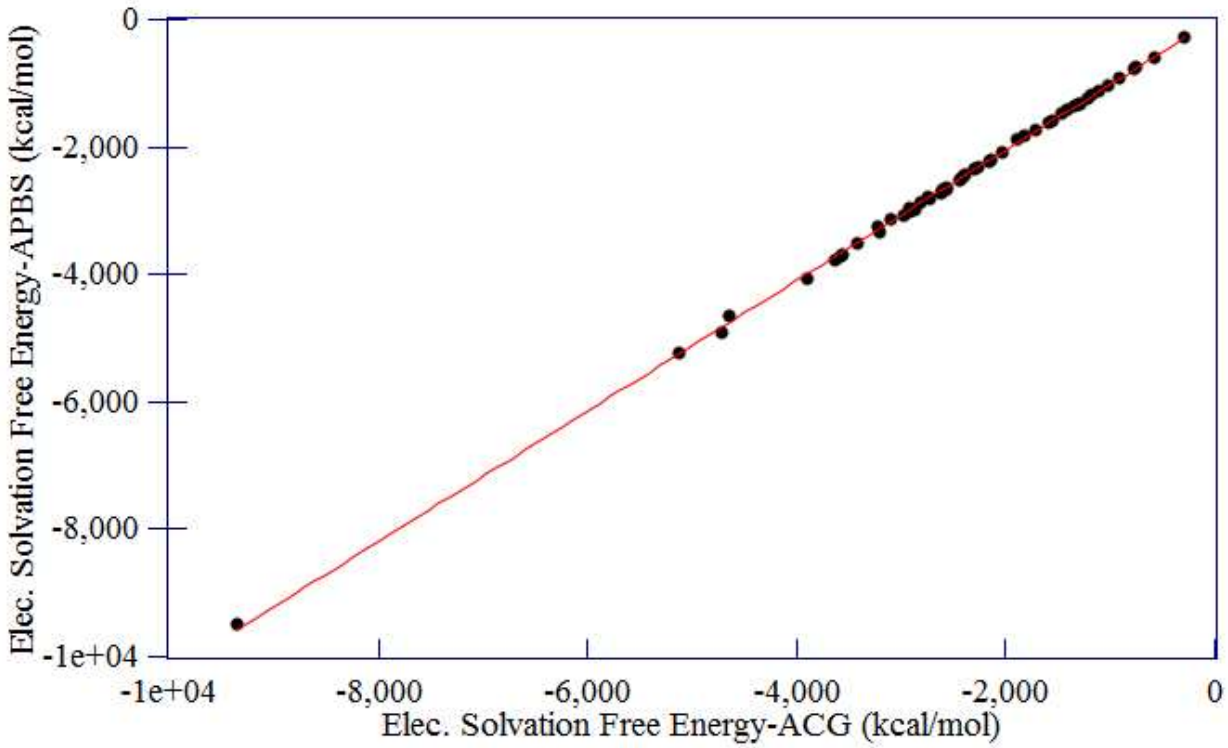

Figure 1. The electrostatic solvation free energy of 55 proteins at 0.5 M NaCl obtained with the APBS and ACG PB solvers. Here only the linear PB results are shown. The red line represents the best fit line through the data points. The slope of this best fit line is 1.0 and the correlation coefficient is R^2=0.9999. The interior and exterior dielectric constants are set to 1 and 78.5, respectively. The temperature of the ionic solution is 298.15 K. The ion exclusion region is not included in these PB calculations. The other parameters used in both PB codes are provided in the text.

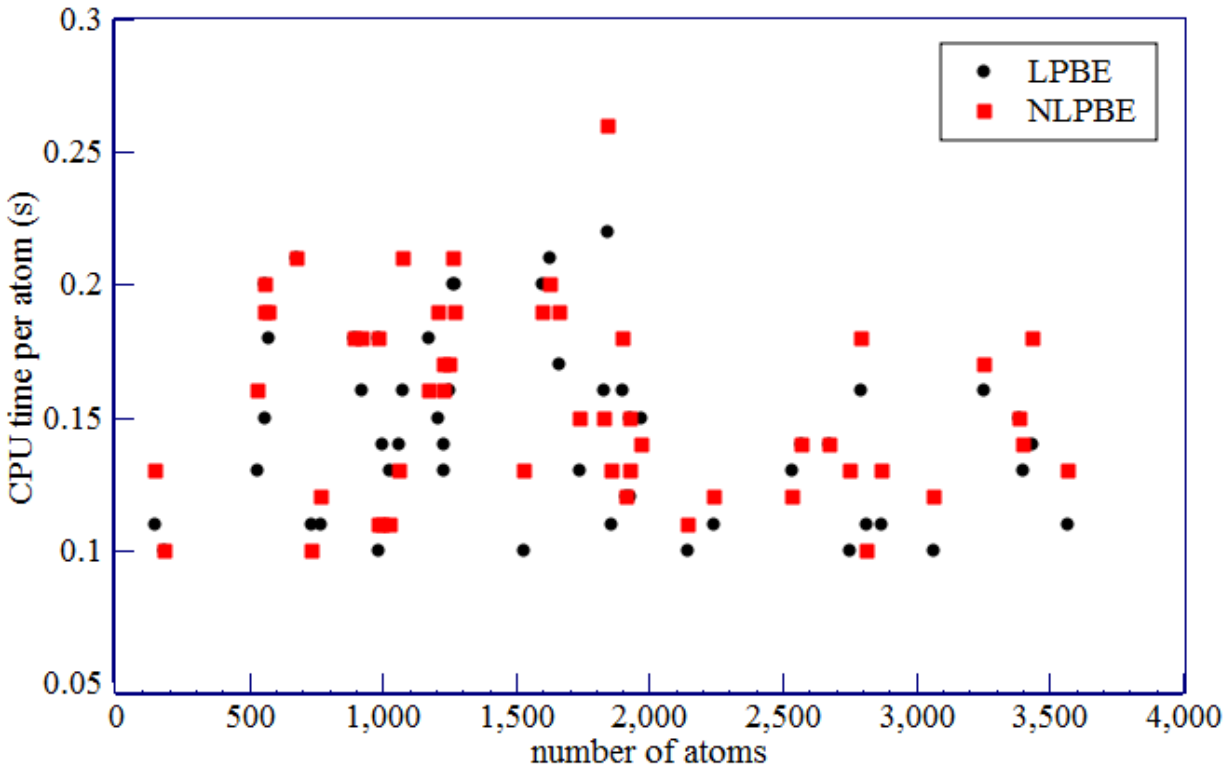

Figure 2. The execution or CPU time for all the 55 proteins divided by the number of atoms as a function of the number of atoms for both nonlinear Poisson-Boltzmann equation (NLPBE) and its linear counterpart (here termed LPBE). These timings refer to the computation of the electrostatic salvation free energy at 0.1 M NaCl.

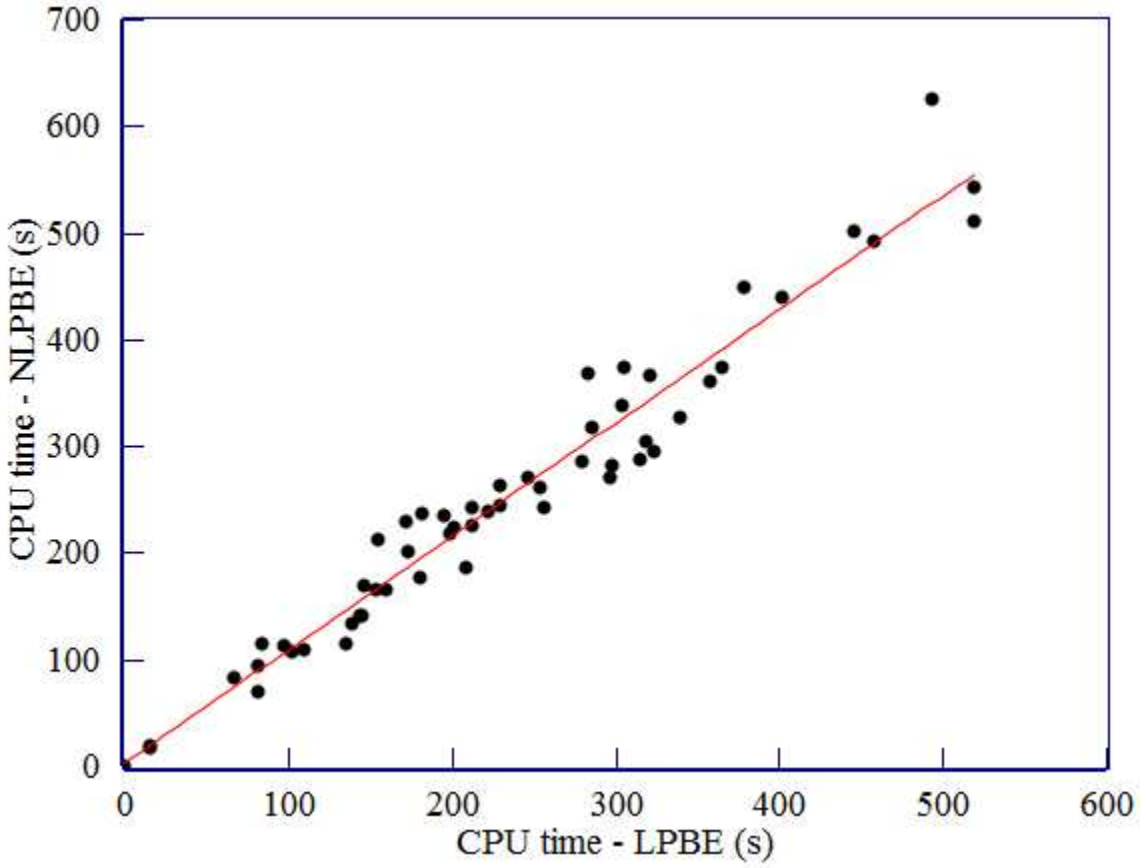

Figure 3. Comparison of the CPU time for all the 55 proteins required using the linear and nonlinear PBE. With a few exceptions, the NLPBE solution takes about the same time as the LPBE. These timings refer to the computation of the electrostatic solvation free energy at 0.1 M NaCl. The red line represents the best fit line through the data points. The slope of this best fit line is 1.06 and correlation coefficient is R^2=0.95.

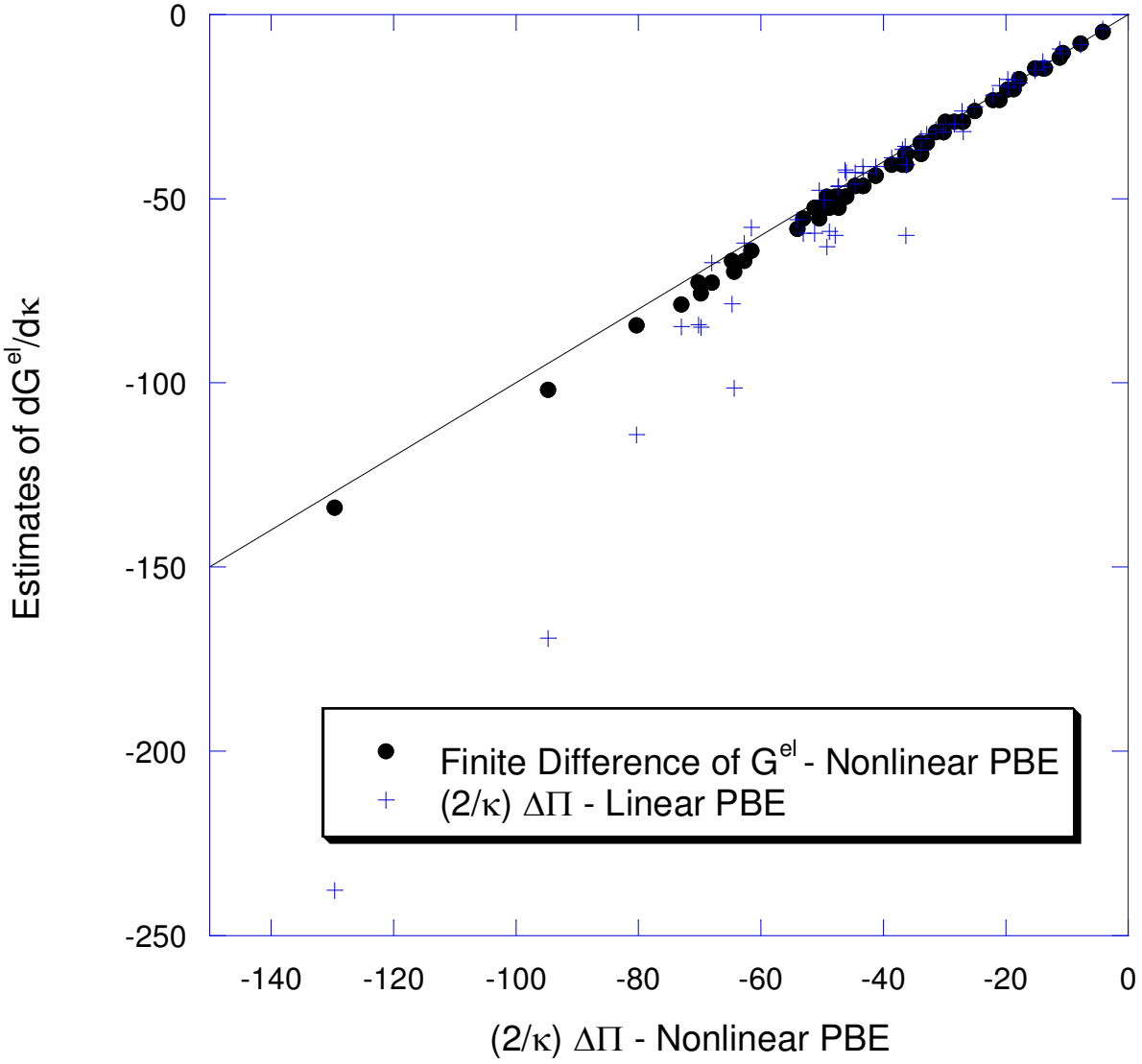

Figure 4. Comparison of the salt sensitivity, $\partial G^{el}/\partial\kappa$, obtained using the osmotic press relation (23) in the main text and the nonlinear PBE against: (i) the finite difference estimate of $\partial G^{el}/\partial\kappa$ using (1) and (ii) the salt sensitivity estimated using the linear PBE. Different points correspond to the proteins listed in Table 1.